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Tuberculosis elimination in the Canadian First Nations population: assessment by a state-transfer, compartmental epidemic model

Michael Clark [a,*], **D. William Cameron** [b]

[a] *Department of Pediatrics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1, Canada*
[b] *Division of Infectious Diseases, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada*

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Summary
Background: Tuberculosis (TB) remains an important public health problem in Canadian Aboriginal (First Nations and Inuit) communities. The objectives of this study were to predict future disease burden and set feasible targets for the elimination of TB in the First Nations population, using retrospective data and an epidemic model.
Methods: Reported TB incidence data (1974—2002), previously published TB meningitis data from the pre-chemotherapy era, and previous estimates of disease risk following infection were used to estimate a trend in the annual risk of infection from 1929 to 2002, and the age-specific prevalence of infection in 2002. A state-transfer, compartmental model was then developed to predict future disease burden. Two scenarios were simulated, with different disease risk parameters.
Results: The estimated prevalence of infection in 2002 was 20.9% in scenario 1 and 25.5% in scenario 2. Predicted incidence rates in 2015 were 16.8 per 100 000 and 11.7 per 100 000 for the two scenarios, respectively. The incidence of disease was not lower than 1 per 100 000 for either scenario in 2034, the arbitrarily chosen last year of the model.
Conclusions: The goal of eliminating TB among Aboriginal peoples in Canada is a feasible one, but will only be achieved with continued investment in programs designed to control and prevent transmission. Reactivation disease cases may occur for a number of years to come, making rapid elimination a difficult goal.

Introduction

Tuberculosis (TB) is an important public health problem in Canadian Aboriginal (First Nations and Inuit) communities. Rates of disease in the First Nations population remain 20—30

* Corresponding author. Tel.: +1 613 884 6278.
E-mail address: mclar018@uottawa.ca (M. Clark).

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times higher than Canadian-born, non-Aboriginal rates.[1–3] At the global level, the Stop TB Partnership and the World Health Organization have developed a plan for TB elimination in the long term, with a focus on intensified measures in high-burden populations.[4] In Canada, a federal government strategy to eliminate TB among First Nations people was implemented in 1992. The original goal of this strategy was to reduce TB incidence to less than one per 1 000 000 by 2010.[5] Many experts considered this target to be unattainable, leading to a review of program goals in 2005. The objective remains TB elimination, although newer more long-term targets for incidence reduction have been endorsed.[6]

Modeling techniques have been used to assess trends in the annual risk of tuberculous infection (ARI) in populations,[7–10] to assess the risk of disease following infection,[11–13] and to estimate the impact of medical and public health interventions on the overall epidemic.[14–17] Using previously published estimates of disease risk[13] and TB case notification data for the period 1974–2002, we estimated two possible ARI trends in the First Nations population between 1929 and 2002. These trends produced two potential scenarios for the age-specific prevalence of infection in 2002, and the risk of disease following tuberculous infection. These data were then applied to a state-transfer, compartmental model to predict future disease burden. The objectives of the study were to predict future disease burden and set feasible targets for TB elimination in the First Nations population. The epidemiology and control of TB in this population is then discussed in the context of our findings.

Methods

Estimation of the age-specific prevalence of infection in 2002

Accurate estimates of the age-specific prevalence of tuberculous infection in the overall First Nations population are lacking. In order to estimate the prevalence of infection by one-year age group in 2002, we used TB case notification data and previously published data on TB disease risks.[13] Age-specific TB case notification data for the First Nations population in Canada ('Status Indians' living on and off reserve) were supplied by Health Canada, for the period 1974–2002. These data (Status Indian TB cases by age group nationally) are available to the public through annual Health Canada reports.[1] Demographic data for the First Nations population living on and off reserve (the 'Indian Registered Population') between 1974 and 2002 were available by one-year age group from the Department of Indian and Northern Affairs Canada. Trends in disease incidence estimated in this study were compared to previously presented data,[2] to assess their accuracy.

Using the 1974–2002 data set, we developed a maximum likelihood model with the following assumptions. First, tallies of disease cases in each age group a and each year t, $D(a,t)$, represent the sum of individuals experiencing disease soon after primary infection $P(a,t)$, endogenous reactivation of latent infection years later $E_n(a,t)$, and disease following exogenous reinfection $E_x(a,t)$, as shown in the following expression:

$$D(a,t) = P(a,t) + E_n(a,t) + E_x(a,t) \quad (1)$$

Age groups in these analyses included ten-year ranges from 15 to 64 years, similar to Sutherland et al.[11] The states $P(a,t)$ and $E_x(a,t)$ occur within one year of a new infection with *Mycobacterium tuberculosis*. The first occurs among persons previously unexposed to infection, while the latter occurs among persons with a longstanding latent tuberculous infection. This approach is similar to that of Dye and colleagues.[17] Assuming that individuals experience risks d_p, d_n, and d_x of developing disease following initial infection, longstanding latent infection, and exogenous reinfection, respectively, the above expression can be rearranged as follows:

$$D(a,t) = I(a,t)d_p + L(a,t)d_n + R(a,t)d_x \quad (2)$$

where $I(a,t)$ is the number of previously uninfected individuals acquiring a new infection within the last year, $L(a,t)$ is the number of people with longstanding latent infection, and $R(a,t)$ is the number of previously infected individuals experiencing re-infection with a new strain of *M. tuberculosis*. Numbers of people in age group A at time t (where A spans the ages a_j, a_{j+1}) in each of the three groups were calculated using estimates of the ARI at different times t ($ARI(t)$) and estimates of the prevalence of infection p among individuals of age a at time t:

$$I(A,t) = \sum_{a=a_j}^{a_{j+1}} ARI(t)\{1 - p_{a-1,t-1}\}n(a,t) \quad (3)$$

$$R(A,t) = \sum_{a=a_j}^{a_{j+1}} ARI(t)\, p_{a-1,t-1} n(a,t) \quad (4)$$

$$L(A,t) = \sum_{a=a_j}^{a_{j+1}} n(a,t)\, p_{a,t} - R(a,t) - I(a,t) \quad (5)$$

where $n(a,t)$ is the number of First Nations people of age a at time t.

The prevalence of infection among individuals of age a at time t was estimated as follows:

$$p_{a,t} = 1 - \exp\left\{-\int_{t-a}^{t} \lambda(u)du\right\} \quad (6)$$

where $\lambda(u)$ is the annual rate of tuberculous infection at time u. This rate is related to the risk of infection at time u by: ARI = $1 - \exp(-(u))$. The risk of tuberculous infection may be age-dependent,[18] although this relationship remains unclear. We assume no age-dependence, similar to the approach of Vynnycky and Fine.[10] Assuming that the infection rate declines at a constant rate r over time, the above expression simplifies to:

$$p_{a,t} = 1 - \exp\left\{\frac{\lambda(t) - \lambda(t-a)}{r}\right\} \quad (7)$$

Using the above data and mathematical equations, two maximum likelihood models (referred to hereafter as 'scenario 1' and 'scenario 2') were developed to estimate the ARI between 1929 and 2002. In scenario 1, risks of disease following infection were allowed to vary within confidence

limits of previously published ranges:[13] 14–29% for d_p, 2.8–9.2% for d_x, and 0.08–0.1% for d_n. In scenario 2, risks of disease were allowed to assume any value between 0 and 1. The ARI trend and values for disease risk were thus estimated by minimizing the following Poisson log-likelihood Chi-square deviance function:

$$D = -2\sum_t \sum_A O_{A,t}\ln(D(A,t)) - O_{A,t}\ln(O_{A,t}) + O_{A,t} - D(A,t) \quad (8)$$

where $O_{A,t}$ is the number of observed (reported) TB disease cases in age group A at time t.

In these analyses, ARI values between 1929 and 1947 were fixed values, based on estimates from previously published tuberculous meningitis data.[13] The ARI then declines at constant rate r after 1947, the year in which streptomycin therapy began in Canada (isoniazid appearing shortly afterwards in the early 1950s),[19] and when TB mortality in the First Nations population began a sharp decline.[20] These methods generate the most likely ARI trend – between 1948 and 2002 – to explain disease incidence between 1974 and 2002, and to give estimates of the prevalence of infection by one-year age category in 2002 through expression 6.

Rates of infectious TB were calculated for the period 1974–2002. TB cases were considered infectious if they were sputum smear and/or sputum culture positive. Infectious TB rates were then matched to ARI estimates for each year from 1974 to 2002, to estimate the number of transmissions per case.

State-transfer compartmental model

Health states and possible transitions in the state-transfer, compartmental model are depicted in Figure 1.

Difference equations for movement between states in the compartmental model are provided below. In the following equations, $U(t,a)$ is written U, while $U(t+1,a+1) - U(t,a)$ is written U'.[17] This applies to the uninfected state, as well as the other states.

$$U' = -\lambda(t)U \quad (9)$$

$$M' = (\lambda(t)(1-(d_p(a)))U - (d_n(a)+\lambda(t)d_x(a))M + (T_i + T_n) \quad (10)$$

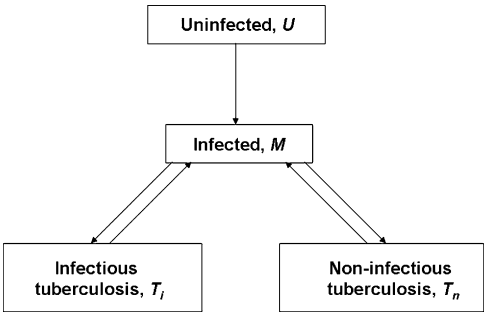

Figure 1 Health states and possible transitions in the state-transfer, compartmental model.

$$T_i' = (\lambda(t)d_p(a))\,f(a)U + (d_n(a) + \lambda(t)d_x(a))\,f(a)M \quad (11)$$

$$T_n' = (\lambda(t)d_p(a))(1-f(a))U + (d_n(a) + \lambda(t)d_x(a))(1-f(a))M \quad (12)$$

The M state includes all those infected with *M. tuberculosis*, similar to the sum of $I(a,t)$, $R(a,t)$, and $L(a,t)$ as described above. In the above expressions, $f(a)$ is the age-specific probability that a TB disease case is infectious to others. We assume that this value is 0 in children aged 0–14 years, while 73% of those aged 15 or more years are assumed to be infectious. Children are generally unable to produce sputum until early adolescence. Although cavitary disease can occur under the age of 15 years, children in this age category are not commonly infectious.[21] The estimate for individuals aged 15 years or more was derived from the TB data set described above. Another simplifying assumption we make is that TB disease cases are all treated and return to the infection state, M. Although case fatality rates in Canada are markedly lower than areas of the developing world, we do recognize that deaths continue to occur.

The number of susceptibles U was assumed to increase by 2% each year, similar to previous population projections.[22] Risks of disease were obtained from the maximum likelihood methods of this study, with two exceptions. We assumed the risk of disease among children aged less than 15 years was 29%,[23] and that the risk of disease in persons aged more than 65 years approximated the risk among 45–64 year-olds.

Outcomes from analyses of the compartmental model included predicted TB disease rates (overall and infectious) by year, for scenarios 1 and 2. Simulations are run

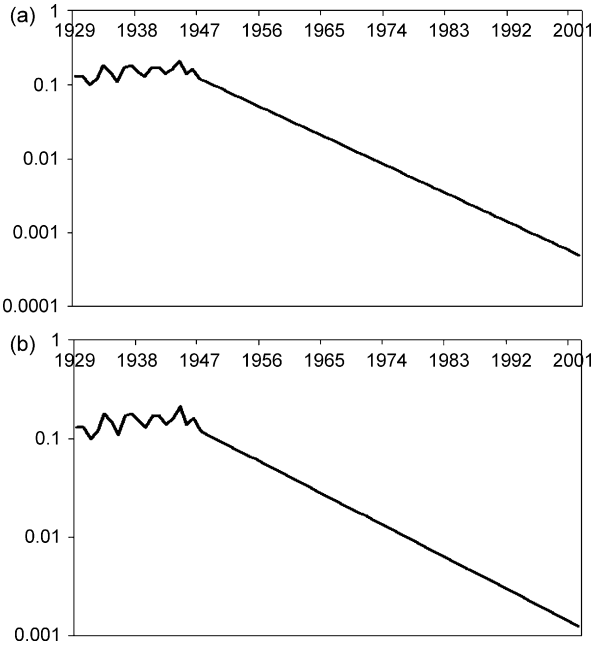

Figure 2 Estimated annual risk of infection (ARI) from 1929 to 2002 using the maximum likelihood model: (a) scenario 1; (b) scenario 2.

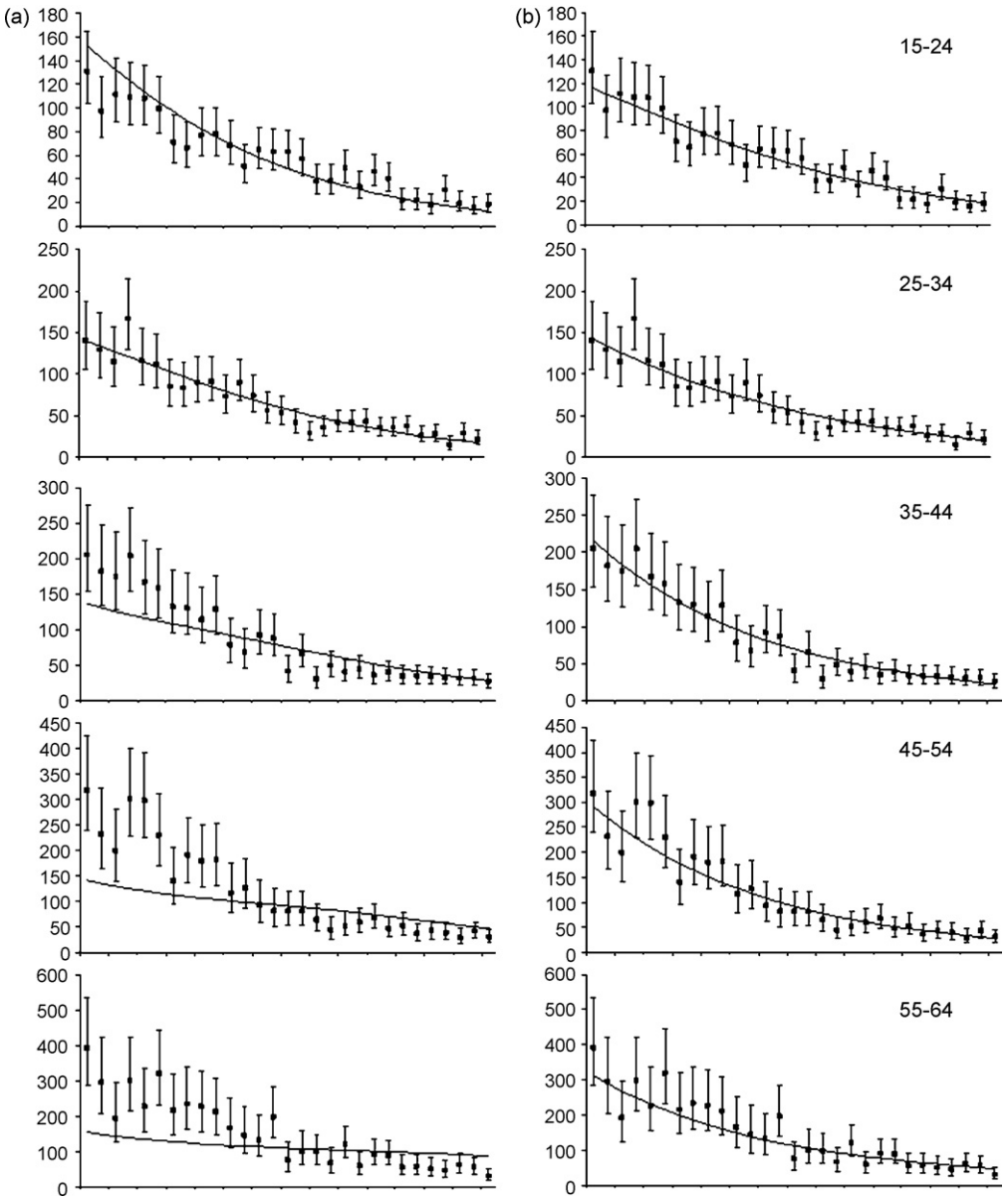

Figure 3 Observed and predicted age-specific TB incidence rates (1974—2002): (a) scenario 1; (b) scenario 2. Markers are observed rates with 95% confidence limits; lines are rates predicted by maximum likelihood model. Age groups (in years) are shown to the right.

until 2034, a year chosen somewhat arbitrarily for graphing purposes. All above analyses were carried out using Microsoft® Excel 2002.

Results

The estimated trends in ARI for scenarios 1 and 2 are shown in Figure 2. Annual rates of decline in the ARI between 1947 and 2002 were 10.5% and 8.6% for scenarios 1 and 2, respectively. Corresponding estimates of the ARI in 2002 were 0.05% and 0.13%. Scenario 1 predicted an overall prevalence of infection of 20.9% in 2002, while scenario 2 resulted in a prevalence of 25.5%. Observed and predicted rates of TB disease incidence by age group are provided in Figure 3. Model predictions of disease incidence in scenario 1 are poor for older age groups, particularly in the 1970s. Predicted age-specific rates fall within 95% confidence limits of observed rates for most years in both scenarios, and the vast majority of data points in scenario 2.

Table 1 contains estimates of disease risk generated from maximum likelihood exercises.

The reported infectious TB rate declined from 100 per 100 000 in 1974 to 13 per 100 000 in 2002 (Figure 4). Estimates of the number of transmissions per infectious case are higher in scenario 2 than in scenario 1. In scenario 1, the number declines from 8.2 per case in 1974 to 3.8 per case in 2002. The number drops from 12.9 to 9.6 over the same period in scenario 2.

Future predictions of TB disease incidence are given in Figure 5. The predicted overall disease rate in 2010 is 20.1 per 100 000 in scenario 1, and 16.2 per 100 000 in scenario 2. In 2015, these rates fall to 16.8 and 11.7 per 100 000, respectively. Rates do not fall below 1 per 1 000 000 — or below 1 per 100 000 — by 2034.

Table 1 Estimated risks of TB disease in scenarios 1 and 2

Risk category	Age	Scenario 1 (%)	Scenario 2 (%)
Disease following initial infection, d_p	15–24	21.1	15.4
	25–34	21.5	17.5
	35–44	21.3	18.8
	45–54	21.6	20.8
	55–64	21.6	21.5
Endogenous reactivation of latent infection, d_n	15–24	8.02×10^{-2}	5.84×10^{-3}
	25–34	8.36×10^{-2}	1.81×10^{-4}
	35–44	8.00×10^{-2}	1.00×10^{-4}
	45–54	8.10×10^{-2}	1.41×10^{-3}
	55–64	9.61×10^{-2}	2.24×10^{-2}
Disease following exogenous reinfection, d_x	15–24	5.23	1.43
	25–34	5.75	9.60
	35–44	6.65	16.6
	45–54	7.48	22.6
	55–64	7.12	22.6

Discussion

To our knowledge, this is the first attempt to estimate future TB disease burden in the Canadian First Nations population, using an epidemic model. We believe this is an important exercise, given that targets previously set for elimination in this population were chosen somewhat arbitrarily. Although we agree that elimination is an important and attainable goal, we also believe it is prudent to set realistic targets for elimination. As one may expect at the tail end of an epidemic curve, the rate of decline in TB incidence has slowed in comparison to earlier years when TB incidence overall was much higher. A similar trend was observed in the overall Canadian population during the second half of the twentieth century.[24] This phenomenon is partly related to the increasing proportion of cases resulting from endogenous reactivation, which are less likely to be prevented through aggressive public health interventions. Reactivation disease can be expected to occur in the First Nations population for a number of years to come.

Several outcomes of the model are reassuring in terms of their plausibility. Similar to expert opinion,[25] our model estimates the prevalence of infection in the Canadian First Nations population was between 20% and 30% in 2000. Annual rates of decline in the ARI between 1947 and 2002 for scenarios 1 and 2 were 10.5% and 8.6%, respectively. These values are similar to estimates from other populations in different studies (Table 2).[7–9,13,26–28] Two

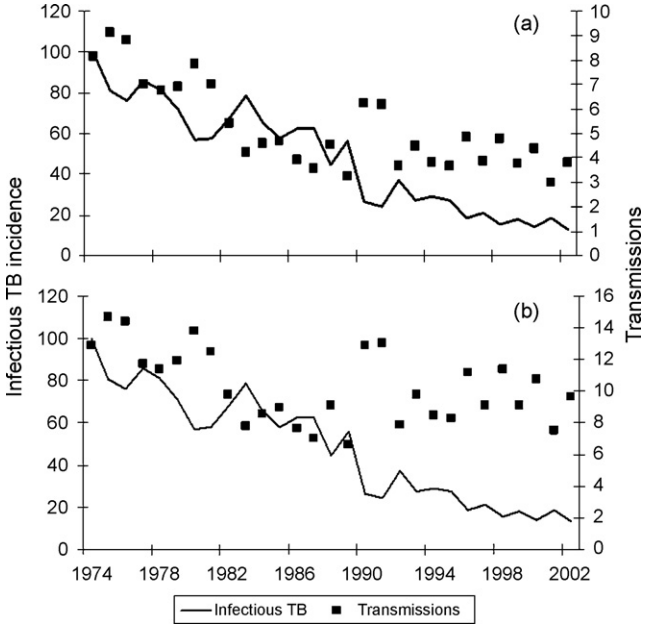

Figure 4 Observed infectious (pulmonary, sputum smear and/or culture positive) TB and estimated number of transmissions per infectious TB case by year (1974–2002): (a) scenario 1; (b) scenario 2. Number of transmissions was estimated by matching risk of infectious TB in each year with annual risk of infection values generated by maximum likelihood model.

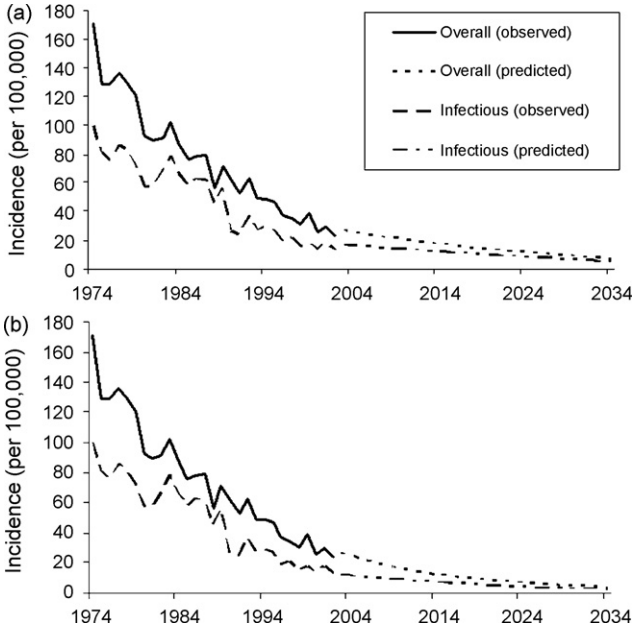

Figure 5 Observed overall and infectious TB rates (1974–2002) and future overall and infectious TB rates (2002–2034) predicted by state-transfer, compartmental model: (a) scenario 1; (b) scenario 2.

Table 2 Estimated annual rates of decline in the annual risk of tuberculous infection in different populations

Population	Time period	Annual rate of decline	Reference
Sweden	1925—1945	9%	9
Netherlands	1940—1966	13%	7
Beijing, China	1950—1995	8%	26
Saskatchewan	1954—1971	11.6%	8
France	1965—1980	10.8%	27
Barcelona, Spain	1975—1991	8%	28
British Columbia First Nations	1979—2000	13.8%	13

recent studies have estimated an ARI of 0.03% in regional First Nations populations, one in 2000[13] and the other in a 1998—2004 birth cohort.[29] In the latter study, a worst-case estimate of 0.22% was also calculated.[29] Our estimates of the ARI in 2002 were 0.05% and 0.13% for scenarios 1 and 2, respectively. These values fall within the above range of estimates, which were calculated from tuberculin skin testing data.

For several reasons, scenario 2 provides a more plausible model to explain disease incidence. First, it predicts observed disease rates during the 1974—2002 period with much greater accuracy (Figure 3). Second, futures rates predicted by this scenario fall almost perfectly onto an exponential trend line fit to the observed rates between 1974 and 2002 (Figure 6). This is what may be expected at the tail end of an epidemic curve,[24] as described above. In this scenario, the number of transmissions per infectious TB case is higher over time (ranging from 12.9 to 9.6 from 1974 to 2002), which is very plausible given the frequency and intensity of TB outbreaks in First Nations communities.[30—32] Estimated risks of reactivation of latent infection in scenario 2 are lower than in scenario 1, although they are closer to values in other studies.[11,12]

Interestingly, risks of disease following exogenous reinfection in scenario 2 are quite high in older age categories, and even exceed risks following primary infection in some cases (Table 1). Although the latter observation may seem implausible, it should be noted that the values are very similar; this may reflect the distant exposure of many elders in these communities, and resultant waning of immunity. In other words, a history of distant infection during the height of the TB epidemic may not confer much protection — if any — against a new infection, particularly among aging people who may have other medical risk factors. Conditions such as diabetes mellitus, renal disease, and malnutrition have been identified as possible risk factors for TB in First Nations individuals,[6] although these relationships have not been explored in depth. There may also be a component of genetic susceptibility in this population, elevating the risk of progression to TB disease.[33]

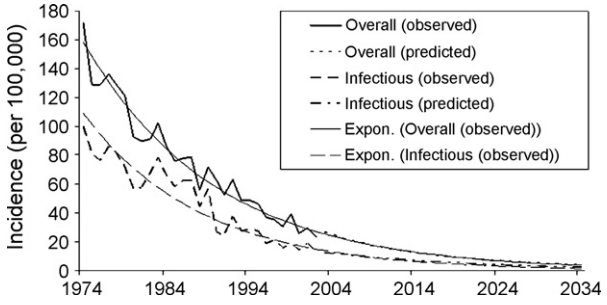

Figure 6 Observed overall and infectious TB rates (1974—2002) and future overall and infectious TB rates (2002—2034) in scenario 2, with exponential trend lines fitted to observed rates.

The main limitation of any modeling exercise is that study findings must be interpreted in light of the model's assumptions. We have based model parameters on observations from the Canadian First Nations population, so that assumptions in the model were at the very least relevant to the study population. Another limitation of this particular model was its simplicity. Other models have considered the impact of vaccination and treatment, along with additional health states such as treatment failure, natural cure, and death. It was not the objective of this study to estimate the potential impact of specific medical or public health interventions, but rather the feasibility of elimination within certain time frames given what we know about the epidemiology of TB in this population.

A reduction to 1 per 1 000 000 people (translating to less than one case in this population of less than 800 000 people) by 2010 is not likely to happen. The potential consequence of an unattainable goal is that successful programs may be improperly evaluated, as they fail to achieve the impossible. Program goals have recently been reviewed and changed, and more realistic long-term targets for incidence reduction and elimination have been set.[6]

Although we did not simulate any specific interventions, one of the key parameters in the model is transmission. Naturally, the degree of transmission and risk of infection in the population will depend upon medical and public health interventions. Elimination will be achieved by continuing to prevent transmission of TB to younger generations, who then in turn carry the bacillus for decades and may one day themselves become transmitters. TB elimination in the Canadian First Nations population will require continued commitment at high levels, throughout the lifetime of several elected governments.

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data available to the public through annual reports prepared by these agencies.

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Ethical approval: The study did not involve review of individual medical records or animal care. The data used in this study were national-level aggregate data available to the public. Ethical approval for the study was not required.

Conflict of interest: The authors have no conflicts of interest to declare.

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